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Critically Ill Patients With HIV
40 Years Later

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The development of combination antiretroviral therapies (cARTs) in the mid-1990s has dramatically modified the clinical presentation of critically ill, HIV-infected patients. Most cART-treated patients aging with controlled HIV replication are currently admitted to the ICU for non-AIDS-related events, mostly bacterial pneumonia and exacerbation of comorbidities, variably affected by chronic HIV infection (COPD, cardiovascular diseases, or solid neoplasms). Today, *Pneumocystis jirovecii* pneumonia, cerebral toxoplasmosis, TB, and other severe opportunistic infections only occur in patients with unknown viral status, limited access to cART, viral resistance, or compliance issues. Acute respiratory failure, neurological disorders, and sepsis remain the main conditions that lead HIV-infected patients to the ICU, although admissions for liver diseases or acute kidney injury are increasing. Case fatality dropped substantially over the past decades, reaching figures of HIV-uninfected critically ill patients with similar demographic characteristics, comorbidities, and level of organ dysfunctions. Several other facets of critical care management have evolved in this population, including diagnostic procedures, cART management at the acute phase of critical illness, and ethical considerations. The goal of this narrative review was to depict the current evidence and emerging challenges for the management of critically ill, HIV-infected patients, almost 40 years following the onset of the AIDS epidemic.

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KEY WORDS: AIDS; antiretroviral therapy; cancer; critical care; mechanical ventilation; opportunistic infections; outcome; *Pneumocystis jirovecii* pneumonia; sepsis; toxoplasmosis

The development of combination antiretroviral therapies (cARTs) providing sustained control of HIV replication stands among the most spectacular medical advances in recent decades. Since the introduction of cARTs in 1996, steady improvements in efficacy and safety have converted HIV infection from a consistently and rapidly fatal disease to a chronic condition requiring long-term care. Whereas cART availability remains a major public health issue in low-income countries,[1] a growing population of HIV-positive patients in Europe and North America now receives the benefits of lifelong cART, including a marked drop in the incidence of opportunistic infections (OIs) and other AIDS-related events and remarkable

ABBREVIATIONS: AFB = acid-fast bacilli; ARF = acute respiratory failure; CAP = community-acquired bacterial pneumonia; CMV = cytomegalovirus; CSF = cerebrospinal fluid; HANA = HIV-associated non-AIDS; IMV = invasive mechanical ventilation; IRIS = immune reconstitution inflammatory syndrome; NAAT = nucleic acid amplification test; PCP = *Pneumocystis jirovecii* pneumonia; PCR = polymerase chain reaction

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improvements in both life expectancy and quality of life compared with the early HIV era.[2,3] Conversely, over time, residual HIV replication and/or long-term cART toxicities may result in HIV-associated non-AIDS (HANA) conditions, of which the most common are atherosclerosis, renal dysfunction, certain neoplasms, and liver diseases.

These changes in the characteristics of the HIV-positive population, together with recent advances in critical care, have dramatically modified the outcomes of HIV-positive patients admitted to the ICU. Critical care practices for HIV-positive patients are changing in various areas, including criteria for ICU admission, diagnostic procedures, cART management at the acute phase of critical illness, and ethical considerations. This narrative review of the literature published since 2005 (Table 1) draws a picture of the current evidence and emerging challenges in the management of critically ill, HIV-positive patients, almost 40 years following the beginning of the AIDS epidemic.

The Continuum of HIV Infection: From Primary Infection to Long-term Immune Recovery Under Antiretroviral Therapy

Acute HIV infection is characterized by a rapid rise in plasma HIV-RNA levels and may be associated with myriad nonspecific clinical signs such as fever, myalgia, disseminated lymphadenopathy, and rash that mimic mononucleosis syndrome.[4] However, severe forms with acute encephalitis or myocarditis have occasionally been reported.[5-7] After 3 to 4 weeks, the viremia level plateaus due to the appearance of HIV-specific antibodies. The disease then becomes chronic, with a gradual decline in $CD4^+$ T cells, resulting in the occurrence of AIDS-defining conditions within 2 to 20 years following seroconversion. Of note, both innate and humoral immune alterations occur upon early HIV infection, explaining the high risk of bacterial infection and TB at this stage. Without cART, HIV infection nearly always progresses to end-stage AIDS with wasting, recurrent OIs, and other ultimately fatal complications (eg, HIV encephalitis).

TABLE 1] Literature Search Methodology

- PubMed search focused on publications from the 2005-2018 period
- Search terms: (1) "HIV" OR "acquired immunodeficiency syndrome" AND "intensive care" OR "critical care" OR "mechanical ventilation" OR "acute respiratory failure" OR "acute respiratory distress syndrome" OR "sepsis" OR "septic shock" OR "bacterial pneumonia" OR "coma" OR "altered consciousness" OR "acute kidney injury" (2) "HIV" OR "acquired immunodeficiency syndrome" AND "intensive care" OR "critical care" AND "antiretroviral therapy" OR "immune reconstitution syndrome"
- Two authors (E. A. and F. B.) reviewed the abstracts and selected and reviewed the full articles
- Additional articles were identified by cross-referencing

In patients with acute infection or established AIDS, cART is imperative. However, cART initiation is beneficial and now recommended upon the early stage of asymptomatic HIV infection.[8] In patients with good treatment adherence, cART rapidly controls HIV replication, thereby elevating the $CD4^+$ T-cell count (ideally $> 500/\mu L$), although substantial interindividual variations exist regarding the pace and magnitude of recovery.[2] Importantly, compared with age- and sex-matched HIV-negative individuals, patients on cART are at higher risk for several HANA conditions such as COPD, coronary artery disease, chronic kidney disease, and solid malignancies (eg, lung cancer).[9-14] Contributors to this risk increase may include smoking, cART-induced alterations in lipid metabolism, and viral coinfections (eg, cytomegalovirus [CMV]). In addition, growing evidence suggests that persistent silent HIV replication in sanctuary sites may cause chronic inflammation, which may be involved in the pathogenesis of HANA conditions.[2,15] A role for intestinal dysbiosis has also been suggested by metagenomics-based studies in patients on cART.[16] Overall, chronic HANA conditions now account for $> 75\%$ of deaths in HIV-positive patients living in Western countries.[17]

Changes in Features, Care, and Survival of Critically Ill, HIV-Positive Patients

At the beginning of the HIV epidemic in the early 1980s, the vast majority of HIV-positive patients admitted to the ICU were young adults with severe OIs, malnutrition, and other complications of end-stage AIDS. Many were unaware of their HIV infection. In-ICU fatality rates were extremely high, reaching 70% to 90% in patients requiring invasive mechanical ventilation (IMV) due to *Pneumocystis jirovecii* pneumonia (PCP).[18,19] Understandably, concern emerged among intensivists regarding the usefulness of ICU admission given this catastrophic prognosis and the lack of therapeutic options for controlling AIDS progression in critical illness survivors.

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The introduction of PCP prophylaxis in the late 1980s induced a first change in the requirement for ICU admission in HIV-infected patients. Next, the pivotal randomized controlled trial published in 1990 by Bozzette et al[20] established the benefit of adjunctive corticosteroid therapy in patients with moderate to severe PCP, with an approximately 50% reduction in day 30 and day 90 mortality rates, prompting intensivists to reconsider the potential benefits of life-sustaining interventions in this population.[21] Soon afterward, cART was introduced, offering hope for effective long-term control of HIV infection and establishing ICU admission as an intercurrent rather than a terminal event.

Table 2 presents selected cohort studies published after 2005.[22-36] With the advent of cART, the baseline characteristics of critically ill, HIV-positive patients changed in two major ways. First, the proportion of patients on cART at ICU admission rose steadily, reaching 70% in some ICUs in the United States and Europe. In recent cohort studies, < 30% of patients had the diagnosis of HIV infection made only following ICU admission. HIV infection should be considered in patients who have not been tested and exhibit a compatible clinical presentation, notably those with at-risk behaviors or limited access to health care owing to socioeconomic impediments, (eg, homeless people, immigrants). Second, both the median age at ICU admission and the prevalence of chronic diseases, including HANA conditions (eg, COPD, coronary artery disease, CKD, liver cirrhosis, non-AIDS-defining malignancies), are increasing,[33,34] in tandem with the changing characteristics of HIV-positive patients. Interestingly, in 3,410 HIV-positive individuals (including 71% on cART) included in the prospective US Veterans Aging Cohort Study (VACS), predictors of ICU admission within 2 years following enrollment (6% of included patients) were a composite index of age, $CD4^+$ T-cell count, viral load, hemoglobin, liver transaminase levels, platelet counts, creatinine, and hepatitis C virus status; hypertension, coronary artery disease, or chronic heart failure; and a history of cancer.[37] This work highlights the growing impact of non-AIDS-related comorbidities on the risk of critical illness in HIV-positive individuals.

Simultaneously, intensive care strategies changed substantially. HIV-positive patients with acute respiratory failure (ARF) benefited from improvements in respiratory support, including noninvasive ventilation, as well as protective ventilation when IMV was required to treat ARDS.[38-40] The role for high-flow oxygen therapy has not been specifically investigated in HIV-positive patients; however, in other immunocompromised populations, high-flow oxygen decreased neither IMV requirements nor day 28 mortality compared with standard oxygenation.[41,42] More recently, encouraging results were obtained by using veno-venous extracorporeal membrane oxygenation to treat HIV-positive patients with refractory ARDS, suggesting a role for this salvage therapy even in patients with severe immunosuppression.[43,44] Advances in the management of sepsis and septic shock have probably benefited these patients at high risk for severe bacterial infection.[45] Finally, policies promoting the early ICU admission of patients with profound immunosuppression, including HIV-positive individuals, have contributed to improve outcomes.

In-ICU mortality rates in cohort studies of HIV-positive patients in the United States and Europe ranged from 16% to 37%, which is similar to the range in unselected ICU patients (Table 2).[24,28-30,33,34,46] For the same organ dysfunction severity, HIV-positive and HIV-negative patients now have similar survival rates,[24] even in situations associated with a high risk of death such as cardiac arrest and ARDS.[47,48] Whether HIV infection worsens the prognosis of sepsis remains unclear.[49,50] However, in a prospective study of patients with sepsis, the HIV-positive and HIV-negative groups were similar in terms of disease severity, plasma levels of host response biomarkers, and survival.[51,52]

Today, most predictors of in-hospital death are not directly related to HIV infection. These predictors include: malignancies; chronic liver disease and hepatitis C virus infection; high critical illness severity indexes; admission for medical rather than surgical reasons; and a need for IMV, vasopressor infusion, and/or renal replacement therapy.[24,25,33,53] HIV-related characteristics such as $CD4^+$ T-cell count, viral load, and previous cART are not independently associated with short-term survival, notably in patients admitted for ARF,[54] coma,[55] or sepsis.[31,49] Current fatality rates for severe AIDS-related PCP do not exceed 20%, a value two to three times lower than in HIV-negative patients with PCP.[56] Moreover, in two studies of ICU patients with severe TB[57] or disseminated toxoplasmosis,[58] HIV infection was associated with higher survival rates compared with other causes of immunosuppression.

Main Reasons for ICU Admission

ARF (40%-60% of all admissions), sepsis (10%-20%), and altered consciousness (10%-20%) remain the most

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TABLE 2] Critically Ill, HIV-Positive Patients in the cART Era: Selected Cohort Studies Published After 2005

Setting and Period (Reference No.)	No. of Patients	Age, y[a]	Prior cART	Inaugural Admission	OI[b]	IMV	RRT	Vasopressors	Mortality
Spain, single ICU, 1997-2003[22]	49	40 (33-47)	31%	31%	81%	NA	NA	NA	54% (hospital)
USA, single ICU, 2000-2004[23]	306	44 (24-72)	33%	NA	21%	68%	NA	NA	21% (hospital)
UK, single ICU, 1999-2005[24]	102	39 (32-44)	37%	30%	67%	62%	19%	NA	24% (ICU) 34% (hospital)
France, single ICU, 1999-2006[25]	284	42 (36-49)	53%	20%	25%	44%	11%	23%	14% (ICU)
Mexico, single ICU, 1996-2006[26]	53	38 ± 10	28%	26%	77%	83%	NA	26%	43% (ICU)
Brazil, single ICU, 1996-2006[27]	278	40 ± 10	45%	38%	81%	55%	NA	NA	55% (ICU) 69% (6 mo)
UK, single ICU, 2001-2006[28]	43	44 (40-60)	56%	0 (0%)	44%	62%	27%	56%	32% (ICU)
The Netherlands, single ICU, 1996-2008[29]	80	43 (23-76)	36%	11%	50%	76%	NA	NA	31% (ICU) 45% (hospital) 53% (1 y) 68% (5 y)
France, single ICU, 1997-2008[30]	98	43 ± 11	44%	8%	25%	59%	15%	51%	37% (ICU) 53% (hospital) 55% (1 y)
Brazil, single ICU, 2006-2008[31]	88	40 (31-47)	45%	28%	70%	60%	18%	24%	49% (hospital)
Taiwan, single ICU, 2001-2010[32]	135	39 (31-50)	36%	44%	NA	78%	8%	36%	37% (ICU) 49% (ICU)
USA, 8 ICUs, 2002-2010[33]	539	54 (48-59)	71%	NA	13%	17%	NA	NA	19% (day 30)
France, 41 ICUs, 2005-2010[34]	2,884	46 (40-52)	NA	NA	25%	52%	15%	27%	16% (ICU) 25% (hospital)
China, single ICU, 2009-2013[35]	122	43 (20-76)	39%	64%	48%	80%	8%	30%	64% (ICU) 66% (ICU)
Uganda, single ICU, 2009-2014[36]	101	38 ± 16	55%	10%	72%	57%	NA	27%	57% (ICU)

cART = combination antiretroviral therapy; IMV = invasive mechanical ventilation; NA = not available; OI = opportunistic infection; RRT = renal replacement therapy.
[a]Median (interquartile range) or mean ± SD, as reported in the original publications.
[b]Main or secondary reason for ICU admission.

common reasons for ICU admission at all stages of HIV infection, although new indications such as acute kidney injury, complicated liver disease, and postoperative care are emerging.[23,24,29,32,33] Overall, OI-related admissions are decreasing steadily, and > 70% of HIV-positive patients are now admitted for bacterial sepsis or other conditions not directly due to AIDS (Table 2).[33,34]

In all HIV-positive patients, the $CD4^+$ T-cell count, which is the most readily available surrogate marker of immunodeficiency, is essential to guide the etiological evaluation, notably in patients with ARF or neurological disorders (Fig 1). Except TB, severe OIs occur almost exclusively in patients with $CD4^+$ T-cell counts $< 200/\mu L$. Some rare life-threatening conditions such as CMV infection or invasive aspergillosis occur chiefly at counts $< 50/\mu L$. Because a transient drop in $CD4^+$ T cells is usual at the acute phase of sepsis, diagnostic algorithms should be based on a recent steady-state count, when available, rather than on the count measured at admission. Other baseline features to consider include a history of OIs at risk for recurrence (eg, TB), a geographical origin that predisposes to specific imported OIs (eg, histoplasmosis), adherence to cART and anti-*P jirovecii* prophylaxis if prescribed, and comorbidities.

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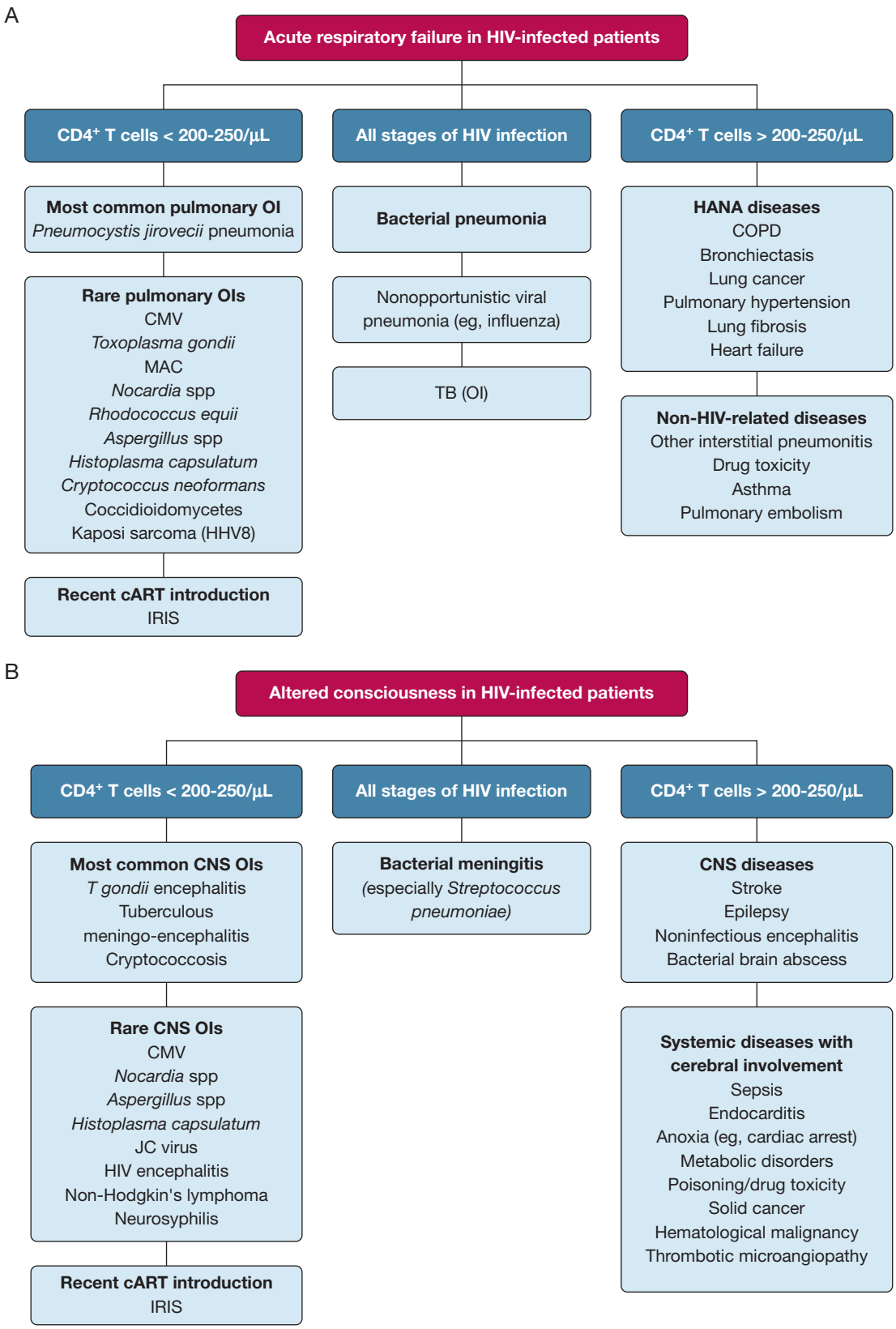

Figure 1 – *Main etiologic diagnoses in HIV-positive patients admitted to the ICU for (A) acute respiratory failure and (B) impaired consciousness. cART = combination antiretroviral therapy; CMV = cytomegalovirus; HANA = HIV-associated non-AIDS; HHV8 = human herpesvirus 8; IRIS = immune reconstitution inflammatory syndrome; MAC = Mycobacterium avium complex; OI = opportunistic infection.*

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Admission for ARF

In HIV-positive patients, community-acquired bacterial pneumonia (CAP) accounts for 35% to 50% of all cases of ARF and is the main reason for ICU admission. The risk of CAP is markedly higher at all stages of HIV infection but is greatest in patients with profound $CD4^+$ T-cell depletion and decreases with cART therapy.[59] *Streptococcus pneumoniae* is the causative agent in 20% to 40% of cases.[54,60] The clinical presentation and outcomes of *S pneumoniae* CAP are the same in HIV-positive patients and in their HIV-negative counterparts matched on demographic characteristics and comorbidities.[61] Bacteremia is more common in HIV-positive patients, probably due to impaired alveolar macrophage and neutrophil functions.[59] *Haemophilus influenzae*, *Staphylococcus aureus*, and Enterobacteriaceae are involved in $< 10\%$ of cases.[54,62] *Legionella pneumophila*, a major pulmonary pathogen in other immunocompromised patients, is rarely responsible for severe CAP in HIV-positive individuals.[54] As with *S pneumoniae* pneumonia, the clinical presentation and prognosis of *L pneumophila* pneumonia do not seem altered by HIV infection.[63] Of note, *Pseudomonas aeruginosa* may cause CAP in patients with very low $CD4^+$ T-cell counts or underlying structural lung damage and should be considered when selecting empirical antibiotics in patients with these risk factors.[31,54,64]

PCP continues to decline in frequency[65] but still accounts for 10% to 20% of ARF cases and remains the most common AIDS-related OI encountered in the ICU, especially in patients without a previous diagnosis of HIV infection.[33-35,54] In HIV-positive patients, PCP manifests as fever, dry cough, and worsening dyspnea culminating in ARF within 2 or 3 weeks. Overall, about one-third of all patients with AIDS-related PCP require initial ICU management.[56,66] Extra-respiratory failures (eg, shock) suggest bacterial coinfection or another concurrent OI. The radiological presentation evolves from reticular infiltrates to diffuse or patchy bilateral ground-glass opacities with alveolar consolidations (Fig 2). According to CT imaging, parenchymal cysts and sparing of subpleural regions are usual at advanced stages of the disease, whereas lymph node enlargement and pleural effusion are not attributable to PCP and should trigger a search for a concurrent OI.

The diagnosis of AIDS-related PCP is far easier than in other immunocompromised patients and relies on the visualization of *P jirovecii* trophozoites or cysts in BAL fluid stained with Gomori-Grocott or Giemsa and immunofluorescence, which has $> 90\%$ sensitivity.[67] Induced sputum is only 50% to 90% sensitive, may be challenging to perform in patients with ARF, and does not allow an exhaustive search for the bacterial or opportunistic coinfections seen in up to 20% of patients with pronounced immunosuppression. The qualitative polymerase chain reaction (PCR) assay is valuable for diagnosing non-AIDS-related PCP,[68] notably in patients receiving prophylactic therapy, but lacks specificity in HIV-positive patients due to their 14% to 69% prevalence of colonization. However, PCR may occasionally be useful in ruling out PCP given its $> 95\%$ negative predictive value.[69] A high fungal load by quantitative PCR supports infection as opposed to colonization[70,71] but seems of limited added value given the high performance of staining and immunofluorescence. Last, blood 1,3 ß-D-glucan elevation (> 80 pg/mL) is highly sensitive (92%-95%) but lacks specificity (78%-82%) because this component of the *P jirovecii* cell wall increases in several other AIDS-related fungal infections (eg, esophageal candidiasis).[72,73] Sulfamethoxazole plus trimethoprim remains the first-line treatment (Table 3). Whether dihydropteroate synthase gene mutations hamper the clinical efficacy of sulfamethoxazole remains controversial,[74] and standard sulfamethoxazole-trimethoprim dosages continue to be recommended in patients with PCP despite prophylaxis.[67] Adjunctive corticosteroid therapy reduces the risk of IMV and in-hospital death, and it should be started within 72 h in all patients with suspected or definite severe PCP ($Pa_{O_2} < 70$ mm Hg while breathing room air).[75]

Pulmonary TB is responsible for up to 10% of ARF cases in Western cohorts of HIV-positive patients and remains a common inaugural AIDS-defining condition,[34] notably in immigrants from endemic areas.[76] The presentation is usually typical at the early stages of HIV infection, whereas patients with $CD4^+$ T cells $< 200/\mu L$ more often have atypical radiological patterns (miliary or diffuse alveolar infiltrates without upper lobe cavitation), extrapulmonary localizations, and no acid-fast bacilli (AFB) visible in sputum smears. Nucleic acid amplification tests (NAATs) should be performed on at least one respiratory sample in all HIV-positive patients with suspected TB, both to distinguish *Mycobacterium tuberculosis* from other mycobacteria in patients with AFB-positive sputum smears and to allow earlier identification of *M tuberculosis* in AFB-negative sputum smears. In this last

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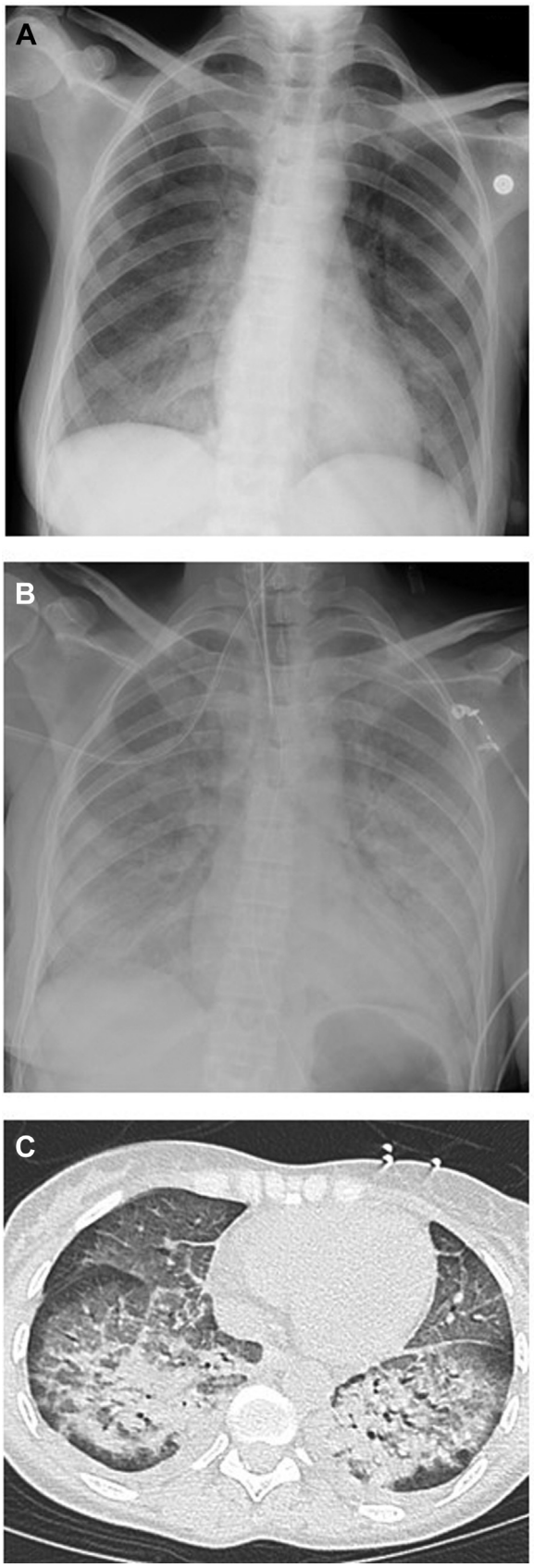

situation, NAAT results are positive in 50% to 80% of patients with culture-proven TB.[67] Some NAATs, such as Xpert MTB/RIF (Cepheid), also detect *rpoB* mutations conferring rifampicin resistance[77,78] several weeks prior to the availability of conventional susceptibility test results. Of note, interferon-gamma release assays may be negative in up to 30% of patients with active TB and should therefore not be used as a pivotal decision-making tool.[67] The first-line regimen for suspected or definite pulmonary TB in HIV-positive patients is a four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (Table 3). A growing amount of evidence supports benefits from corticosteroids in ARF due to TB[79,80]; however, data from HIV-positive patients are lacking, and this adjunctive treatment is currently recommended only in patients with involvement of the CNS or pericardium.

A vast array of other pulmonary AIDS-related diseases may cause ARF in patients with $<$ 50 to 100/μL $CD4^+$ T cells, albeit only very rarely. Examples include non-TB mycobacterial diseases (eg, *Mycobacterium avium* complex), pneumonia due to opportunistic bacteria (eg, *Rhodococcus equi* or *Nocardia* species) or fungi (eg, *Aspergillus* species, *Cryptococcus neoformans*, *Histoplasma capsulatum*, coccidioidomycosis, and mucormycosis), disseminated toxoplasmosis, and Kaposi sarcoma (Fig 1A). Also, CMV has been detected by molecular assays in 5% to 10% of patients with PCP or another OI. However, CMV pneumonitis seems rare; it should be diagnosed only in patients with nuclear inclusions in BAL fluid or lung biopsy specimens or with diffuse interstitial infiltrates or other suggestive patterns by chest CT imaging (eg, ground-glass opacities, focal consolidation, parenchymal micronodules).[67]

The prevalence of ARF due to causes other than bacterial pneumonia and AIDS-related OIs may increase in the near future due to the development of respiratory HANA conditions in aging cART-treated patients with $CD4^+$ T-cell counts $>$ 200/μL. More specifically, COPD, lung cancer, and pulmonary hypertension are becoming

Figure 2 – *A-C, Radiologic presentation of severe* Pneumocystis jirovecii *pneumonia. Severe* P jirovecii *pneumonia in a 44-year-old HIV-positive woman with poor adherence to combination antiretroviral therapy ($CD4^+$ T-cell count at admission, 35/μL). A, Chest roentgenogram at hospital admission: diffuse interstitial infiltrate with alveolar opacities in the lower lobes. B, Chest roentgenogram at ICU admission 3 days later: diffuse alveolar infiltrates. C, Chest CT scan on ICU day 2: diffuse ground-glass opacities with focal alveolar consolidations; note the thickened septal lines, relative sparing of the subpleural regions, and absence of pleural effusion.*

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TABLE 3] Treatments for the Most Common OIs in Critically Ill, HIV-Positive Patients: Guidelines From the Centers for Disease Control and Prevention, the National Institutes of Health, and the Infectious Diseases Society of America

OI	First-line Regimen for Severe Cases	Main Alternatives	Adjunctive Therapies	Timing of cART Introduction
PCP pneumonia	• TMP (15-20 mg/kg/d) and SMX (75-100 mg/kg/d) IV q6h or q8h • Switch to PO after clinical improvement • Total treatment duration: 3 wk (then switch to secondary prophylaxis dosing[a]) • No leucovorin supplementation[b]	Pentamidine 4 mg/kg IV once daily (patients with TMP or SMX adverse events such as allergy or hemolysis due to glucose-6-phosphate dehydrogenase deficiency)	• Corticosteroids if $Pa_{O_2} < 70$ mm Hg (room air) • Prednisone PO: Days 1-5: 40 mg bid Days 6-10: 40 mg daily Days 11-21: 20 mg daily • Alternative: methylprednisolone IV (75% of prednisone dose)	Within 2 wk
TB (drug-susceptible *Mycobacterium TB*)	• Intensive phase (2 mo): isoniazid + rifampin or rifabutin + pyrazinamide + ethambutol • Continuation phase: isoniazid + rifampin or rifabutin • Total treatment duration: Pulmonary TB: 6-9 mo Extrapulmonary TB with CNS involvement: 9-12 mo Extrapulmonary TB with bone or joint involvement: 6-9 mo Extrapulmonary TB at other sites: 6 mo	Consult an infectious disease specialist	• CNS disease: dexamethasone 0.3-0.4 mg/kg/d for 2-4 wk, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg/d and taper by 1 mg/week; total duration of 12 wk • Pericardial disease: prednisone or prednisolone (eg, 60 mg PO daily with weekly tapering over 6 wk)	• Active TB without CNS involvement: Within 2 wk for patients with $CD4^+$ T cells $< 50/\mu L$ Within 8 wk for patients with $CD4^+$ T cells $\geq 50/\mu L$ • Active TB with CNS involvement: deferred initiation (high risk of severe IRIS) • Close collaboration with infectious disease specialists
Toxoplasmosis	• Pyrimethamine 200 mg PO once then pyrimethamine 50-75 mg PO daily + sulfadiazine 1,000-1,500 mg PO q6h + leucovorin 10-25 mg PO daily • Total treatment duration: at least 6 wk (then switch to chronic maintenance therapy[a])	• Pyrimethamine (with leucovorin) plus clindamycin 600 mg IV or PO q6h • TMP 5 mg/kg and SMX 25 mg/kg IV or PO bid	• Corticosteroids if cerebral lesions with mass effect • Anticonvulsants only if seizures (no primary prevention)	No recommendation, due to insufficient data (usually within 2 to 3 wk)
Cryptococcus infections	• Induction therapy (at least 2 wk): liposomal amphotericin B 3-4 mg/kg IV daily plus flucytosine 25 mg/kg qid • Consolidation therapy (at least 8 wk) following clinical improvement and sterilization of CSF	Induction therapy: fluconazole (400-800 mg/d) may replace either liposomal amphotericin B or flucytosine	Corticosteroids may be deleterious in patients with CNS disease and are not recommended	• CNS involvement: 2 to 10 wk following initiation of specific therapy (longer delay if high intracranial pressure) • Other localizations: 2 to 4 wk following initiation of specific therapy

(Continued)

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TABLE 3] *(Continued)*

OI	First-line Regimen for Severe Cases	Main Alternatives	Adjunctive Therapies	Timing of cART Introduction
	cultures: fluconazole 400 mg PO or IV once daily • Maintenance therapy (at least 1 y): fluconazole 200 mg PO			
Histoplasmosis	• Induction therapy (at least 2 wk): liposomal amphotericin B 3 mg/kg/d IV • If confirmed meningitis: increase dosage to 5 mg/kg/d and extend induction to 4-6 wk • Maintenance therapy: itraconazole 200 mg PO tid for 3 days, then bid for at least 12 mo	Fluconazole (400 md/d PO) may replace itraconazole for long-term suppressive therapy	…	As soon as possible
Disseminated MAC disease	• Clarithromycin 500 mg PO bid + ethambutol 15 mg/kg PO daily or azithromycin 500-600 mg + ethambutol 15 mg/kg PO daily • Addition of a third or fourth drug (rifabutin, amikacin, fluoroquinolone) should be considered for patients with $CD4^+$ T cells $< 50/\mu L$, high mycobacterial loads (> 2 log CFU/mL of blood), or in the absence of effective cART	Consult an infectious disease specialist	…	After completion of the second week of MAC-directed therapy
CMV infection	• Ganciclovir 5 mg/kg IV q12h • Role of oral valganciclovir: not established • Optimal treatment duration: not established	Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h	…	No recommendation, due to insufficient data (usually within 2 wk)
PML	cART	…	…	As soon as possible

CMV = cytomegalovirus; CSF = cerebrospinal fluid; IRIS = immune reconstitution inflammatory syndrome; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis jirovecii* pneumonia; PML = progressive multifocal encephalopathy (due to JC virus); PO = per os; SMX = sulfamethoxazole; TMP = trimethoprim. See Table 2 legend for expansion of other abbreviations. (Data from Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America.[67])

[a]Consider discontinuation in patients with $CD4^+$ T cells $> 200/\mu L$ under cART.

[b]Leucovorin supplementation does not efficiently prevent myelosuppression and may be associated with treatment failure.

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increasingly common.[34] In these patients, the diagnostic evaluation does not differ from that in HIV-negative patients (Fig 1A).

Admission for Neurological Disorders

The incidence of AIDS-related diseases involving the CNS has dropped sharply in high-income countries since the introduction of cART.[67] In a single-ICU study, AIDS-related diseases accounted for only 42% of admissions for altered consciousness, with the most common diagnoses being cerebral toxoplasmosis, tuberculous meningitis, and cryptococcal meningitis.[55] Other OIs such as CMV encephalitis, progressive multifocal leukoencephalitis due to JC virus, CNS non-Hodgkin's lymphoma, neurosyphilis, cerebral aspergillosis, nocardiosis, and histoplasmosis are exceedingly rare causes of neurological failure in HIV-positive patients (Fig 1B).[34,55] Contrast-enhanced CNS imaging (preferentially MRI) is a key component of the diagnostic evaluation in patients with deep $CD4^+$ T-cell depletion and must be performed prior to lumbar puncture to rule out a mass effect responsible for a high risk of cerebral herniation.

AIDS-related cerebral toxoplasmosis is nearly always due to reactivation of latent intraparenchymal *Toxoplasma gondii* cysts rather than to the primary infection. In a multi-ICU study, altered consciousness, focal deficits, and seizures were observed in 67%, 59%, and 22% of patients, respectively, whereas fever was absent in almost one-half of the cases.[81] Brain MRI shows multifocal, ring-enhanced, and sometimes hemorrhagic lesions in the cortex and/or basal ganglia region with a mass effect from peripheral edema that may require corticosteroid therapy.[82] Solitary lesions and diffuse encephalitis are far less common. The PCR assay for *T gondii* in cerebrospinal fluid (CSF) is highly specific (> 95%) but is no more than 50% sensitive after a few days of therapy. *T gondii* PCR in blood is even less sensitive but may provide valuable information if positive in a patient with contraindications to lumbar puncture. The first-line regimen for suspected cerebral toxoplasmosis is combined pyrimethamine, sulfadiazine, and leucovorin (Table 3). The diagnosis must be confirmed by a clinical and radiological response to empirical toxoplasmosis therapy within 10 to 14 days. A brain biopsy should be considered promptly in patients who fail to respond, have negative IgG serology or PCR results, or have imaging study findings suggesting another etiology (notably CNS lymphoma).[67] Of note, disseminated disease with septic shock, multiorgan failure, myocarditis, and lymphohistiocytic syndrome seem less common in patients with AIDS compared with those with other causes of immunodeficiency.[58]

Tuberculous meningitis is present in up to 20% of HIV-positive patients admitted to the ICU with active TB.[57] The clinical presentation is usually subacute and may include fever, headache, focal abnormalities, consciousness impairments, and seizures. Meningeal inflammation in a predominantly basal location, tuberculomas, hydrocephalus, and vasculitis are common MRI patterns, whereas CSF analysis usually shows lymphocytic pleocytosis with variable cell counts (10-500/μL), low glucose levels, and elevated protein levels (0.5 to > 3 g/L).[83] The low mycobacterial inoculum translates into poor sensitivities of CSF staining (10%-20%), cultures (approximately 70%), and NAATs (approximately 50%). However, NAAT results are highly specific (> 95%) and may remain positive for days following the empirical initiation of TB treatment, thus documenting the diagnosis in patients without initial CSF sampling.[82,84] A large volume of CSF (ie, > 4-5 mL) should be sampled to improve culture sensitivity.[85] The first-line regimen combines rifampicin, isoniazid, ethambutol, and pyrazinamide. No convincing evidence exists that intensified therapies including fluoroquinolone or high-dose rifampicin are clinically beneficial.[86] Adjunctive corticosteroid therapy (dexamethasone 0.3-0.4 mg/kg per day for 2 to 4 weeks, followed by tapering, for a total of 12 weeks) should be considered routinely given the evidence of lower short-term mortality rates in patients with tuberculous meningitis,[67] with no decrease, however, in the prevalence of residual neurological impairments in survivors.[87]

Most cases of cryptococcal meningitis and meningoencephalitis are due to the ubiquitous species *C neoformans*, although *Cryptococcus gattii* infections also occur in subtropical regions. Patients present with fever, headaches, and impaired mental status due to intracranial hypertension. Moderate lymphocytic pleocytosis, mild protein elevation, low to normal glucose levels, and encapsulated yeasts according to Gram or Indian ink staining are the most common CSF findings. CSF cultures are positive in > 90% of patients.[82] Cryptococcal antigen test results on CSF and serum are both sensitive and specific and allow earlier confirmation of the diagnosis, including in cases of disseminated disease. An initial combination of amphotericin B and flucytosine is recommended for at least 2 weeks,[88] followed by an azole-based consolidation

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regimen after clinical improvement and CSF culture sterilization (Table 3).[67] Adjunctive corticosteroid therapy does not appear beneficial and may even be deleterious in this indication.[89] CSF depletion by repeated lumbar punctures is an essential component of care in patients with intractable intracranial hypertension due to severe forms of the disease.

The diagnostic evaluation for neurological failure is similar in cART-treated patients with $CD4^+$ T cells $> 200/\mu L$ and in HIV-negative patients (Fig 1B). Nonetheless, intensivists should keep in mind the high risk of bacterial meningitis (notably due to *S pneumoniae*) in HIV-positive patients.[90] Also, stroke may become an increasingly common reason for ICU admission, as an independent association has been reported between long-term HIV infection and stroke due to accelerated vascular senescence.[91]

Admission for Sepsis

Sepsis remains a major reason for ICU admission in HIV-positive patients.[25,32,50] HIV infection increases the risk not only of bacterial pneumonia and meningitis but also of skin and soft tissue infections, notably due to community-acquired methicillin-resistant *S aureus* in endemic areas (eg, USA300 strain in North America) due to a combination of both immune impairments and social risk factors.[92] HIV-positive patients are also at increased risk of primary bloodstream infection due to non-typhi *Salmonella* species, *S aureus*, and *Escherichia coli*, whose incidence correlates with the depth of immunodeficiency.[93] Other severe bacterial infections such as endocarditis or urinary tract infection are also more common in patients with advanced HIV infection.[94] The management of sepsis in HIV-positive patients has no specific characteristics and should follow general guidelines.[45] However, the higher risk of infection by multidrug-resistant bacteria due to repeated antibiotic exposure and frequent contacts with the health-care system should be considered when selecting empirical antimicrobial agents. Septic shock and multiorgan failure occur occasionally during the course of disseminated OIs, notably toxoplasmosis, TB, and histoplasmosis. These infections commonly trigger hemophagocytic lymphohistiocytosis, which may substantially worsen organ dysfunctions.[95] Lastly, *Clostridioides difficile* (formerly *Clostridium difficile*) infection is the leading cause of bacterial diarrhea in HIV-positive patients.[96] However, it remains unclear whether HIV infection is associated with an increased incidence of severe presentations or adverse outcomes.[97]

Antiretroviral Therapy Management in Critically Ill Patients

Immune Reconstitution Inflammatory Syndrome

Immune recovery may induce paradoxical worsening of an already treated or previously undiagnosed OI within weeks or months following initiation of cART. Typical examples include the occurrence of ARF in patients with an initially mild to moderate pulmonary OI (eg, PCP with no baseline indication for corticosteroids) or neurological deterioration due to the enlargement of cerebral tuberculomas or cryptococcal lesions. Immune reconstitution inflammatory syndrome (IRIS) has an estimated crude incidence of 16%, and the main risk factors are a high baseline viral load, low baseline $CD4^+$ T-cell count, and rapid $CD4^+$ T-cell count elevation following initiation of cART.[98]

IRIS drives substantial morbidity and mortality, with a fatality rate of up to 20% in patients with cryptococcal meningitis.[98] IRIS as the main reason for ICU admission was uncommon in recent cohorts of critically ill, HIV-positive patients,[24,25,32] suggesting better anticipation and management by infectious disease specialists. Nonsteroidal antiinflammatory drugs and corticosteroids are the cornerstones of therapy for severe IRIS.[99]

Starting cART at the Acute Phase of Critical Illness

Early cART initiation reduces all-cause mortality and the incidence of new AIDS-defining conditions in noncritically ill, HIV-positive patients with an active OI, notably those with PCP or pulmonary TB and $< 50/\mu L$ $CD4^+$ T cells.[100-103] Accordingly, US guidelines now recommend considering cART initiation within 2 to 3 weeks following the start of OI-directed therapies, except for patients with neurological TB or cryptococcosis, in whom the marked risk of severe IRIS counterbalances potential benefits from prompt immune recovery (Table 3).[67] In contrast, whether antiretroviral drugs should be introduced in cART-naive patients admitted to the ICU for an active OI remains debated. A few retrospective single-ICU studies suggest that early cART initiation may improve both short- and long-term survival rates.[27,30,104] A meta-analysis found that initiation or maintenance of cART in the ICU was associated with a lower short-term risk of death (random effects OR, 0.53; 95% CI, 0.31-0.91; $P = .02$); however, heterogeneity was high ($I^2 = 77\%$), precluding firm conclusions.[105] Given the declining incidence of ICU admissions for inaugural OIs, it is unlikely that a large-scale, randomized controlled trial could solve this

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TABLE 4] Important Considerations for cART Management in ICU Patients

Drug	Most Common Severe Toxicities	Main Drug-Drug Interactions to Consider in the ICU	Alternatives for Administration in the ICU	Dosage Adjustment if Renal Failure
Nucleoside/nucleotide reverse transcriptase inhibitors				
Abacavir	Hypersensitivity syndromes in patients with HLA-B*5701	…	Liquid formulation	No (avoid if end-stage renal failure)
Emtricitabine	Neutropenia	…	Liquid formulation, crushable pills	Yes
Lamivudine	Rash	…	Liquid formulation, crushable pills	Yes
Zidovudine	Lactic acidosis, myopathy, bone marrow toxicity, hepatitis	Rifamycins, valproic acid, fluconazole	Liquid formulation, crushable pills, IV formulation	Yes
Tenofovir	Nephrotoxicity (proximal tubular acidosis with Fanconi-like syndrome, acute renal failure), rash, hepatitis	…	Crushable pills	Yes
Nonnucleoside reverse transcriptase inhibitors				
Efavirenz	Hepatitis, rash	Rifamycins, voriconazole, posaconazole, phenytoin, phenobarbital, carbamazepine, calcium channel blockers, statins, warfarin, midazolam	Crushable pills	No
Etravirine	Bone marrow toxicity, hypersensitivity syndromes, hepatitis	Rifamycins, fluconazole, voriconazole, posaconazole, phenytoin, phenobarbital, carbamazepine, digoxin, amiodarone, warfarin, statins, clopidogrel, dexamethasone	Crushable pills	No
Nevirapine	Neutropenia, hypersensitivity syndromes, hepatitis	Rifampicin (switch to rifabutin), fluconazole, warfarin	Liquid formulation	Yes
Rilpivirine	Bone marrow toxicity, hepatitis, rash	Rifamycins, PPIs, anti-H2, phenytoin, phenobarbital, carbamazepine, dexamethasone	IV formulation	No
Integrase inhibitors				
Raltegravir	Rash	Rifampicin	Liquid formulation, crushable pills	No
Dolutegravir	Rash, hepatitis	Rifampicin, phenytoin, phenobarbital, carbamazepine, apixaban, metformin	Crushable pills	No

(Continued)

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TABLE 4] *(Continued)*

Drug	Most Common Severe Toxicities	Main Drug-Drug Interactions to Consider in the ICU	Alternatives for Administration in the ICU	Dosage Adjustment if Renal Failure
Protease inhibitors (all ritonavir-boosted)				
Atazanavir	Hyperbilirubinemia, renal lithiasis, QT prolongation	Rifamycins, voriconazole, PPIs, phenytoin, phenobarbital, carbamazepine, fentanyl, midazolam, calcium channel blockers, amiodarone, warfarin, statins	…	No
Darunavir	Rash, peripheral neuropathy	Rifamycins, voriconazole, fluconazole, posaconazole, phenytoin, phenobarbital, fentanyl, midazolam, calcium channel blockers, beta-blockers, amiodarone, digoxin, warfarin, apixaban, rivaroxaban, dabigatran, ticagrelor, metformin, statins, salmeterol	Liquid formulation	No
Fosamprenavir	Rash	Rifamycins, phenytoin, phenobarbital, fentanyl, midazolam, amiodarone, statins, warfarin	Liquid formulation	No
Lopinavir	QT prolongation, bone marrow toxicity, hypersensitivity syndromes, hepatitis	Rifamycins, voriconazole, phenytoin, phenobarbital, valproic acid, fentanyl, midazolam, calcium channel blockers, amiodarone, digoxin, warfarin, rivaroxaban, statins, salmeterol	Liquid formulation	No
Tipranavir	Hepatitis, rash	Rifamycins, voriconazole, phenytoin, phenobarbital, carbamazepine, fentanyl, midazolam, PPIs, amiodarone, digoxin, warfarin, statins	Liquid formulation	No
Fusion inhibitors				
Enfuvirtide	Myalgia, lung toxicity, peripheral neuropathy, pancreatitis, renal lithiasis	…	Subcutaneous formulation	No
CCR5 inhibitors				
Maraviroc	Anemia, rash	Rifamycins, phenytoin, phenobarbital, carbamazepine	Liquid formulation	Yes

Constructed from US Food and Drug Administration approval documents and the French CNS-ANRS guideline documents for the management of cART in HIV-infected patients (available at www.cns.sante.fr). ANRS = National Research Agency on AIDS and Viral Hepatitis; CCR5 = C-C chemokine receptor type 5; CNS = National Committee for AIDS and Viral Hepatitis; PPIs = proton-pump inhibitors.

issue in the near future. Therefore, the appropriateness of starting cART in the ICU should be discussed on a case-by-case basis, in a framework of strong collaboration between intensivists and infectious disease specialists.[106]

Continuing cART in Previously Treated Patients

Stopping cART in virally suppressed patients increases the probability of breakthrough OIs and all-cause death.[107] Consequently, cART should be continued in the ICU whenever possible. The possible emergence of resistant HIV mutants (requiring new genotyping prior to cART reintroduction) should also be considered, although the risk is presumably limited following a brief treatment-free period.

In critically ill patients, factors that may complicate the continuation of cART include side effects, impaired enteral absorption, galenic issues in patients fed via a nasogastric tube, drug-drug interactions, and impaired renal clearance (Table 4). However, a number of solutions exist, such as switching to liquid drug formulations, dosing adjustment based on plasma level monitoring, and, occasionally, parenteral administration. Of note, severe cART-related toxicity may account for up to 6% of ICU admissions in patients on cART.[30,35] Again, close cooperation with infectious disease specialists is fundamental when deciding to continue, modify, or interrupt cART during the ICU stay.

Research Agenda

Several domains should be explored to further improve the management of critically ill, HIV-positive patients. First, there is a crucial need for longitudinal studies of the long-term impact of critical illness on HIV-specific care, progression of HANA conditions, cognitive decline, functional status, and quality of life. Second, the conversion of HIV infection to a chronic manageable disease has ethical implications. Major interventions such as IMV, vasopressor therapy, and renal replacement therapy are now equally used in HIV-positive and HIV-negative ICU patients (Table 2). Although palliative care is an essential component of the management of aging HIV-positive patients with multiple comorbidities,[108] the determinants of end-of-life decisions in the specific setting of critical illness have not been reappraised in detail. Third, solid and hematological malignancies act as new immunosuppression vectors in patients with controlled HIV replication.[34] How the coexistence of malignancy may influence the management, and post-ICU outcomes of HIV-positive patients deserves to be addressed specifically. Along this line, solid organ transplantation is increasingly performed in selected HIV-positive patients with end-stage renal or heart failure, who have similar graft outcomes and survival rates to those seen in HIV-negative patients.[109,110] The reasons for and prognosis of ICU admission have not yet been investigated in this emerging subpopulation of HIV-positive patients.

Conclusions

ICU admission for life-threatening OIs continues to occur in patients with previously undiagnosed HIV infection or with failure to respond to cART due to viral resistance or poor adherence. However, HIV-positive patients with controlled viral replication and $CD4^+$ T-cell counts $> 200/\mu L$ under cART account for a growing proportion of ICU admissions; the main reasons are for bacterial pneumonia and exacerbation of chronic HANA conditions. Regardless of the depth of immunodeficiency, HIV-positive patients now tend to have similar hospital survival rates as HIV-negative ICU patients with the same comorbidities, reasons for admission, and severity of organ failures. Hence, HIV status should no longer be viewed as a pivotal criterion for ICU admission decisions; these decisions should instead be based on frailty, performance status, comorbidities, and other clinical features associated with mid- and long-term outcomes, as with all critically ill patients. Studies focusing on cART use in the ICU, emerging immunodeficiency patterns (eg, malignancies and solid organ transplantation), ethical issues, and the long-term prognosis are needed to fill current gaps in knowledge.

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References

1. Harries AD, Suthar AB, Takarinda KC, et al. Ending the HIV/AIDS epidemic in low- and middle-income countries by 2030: is it possible? *F1000Res* 2016; 2016;5:2328.
2. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. *Lancet*. 2013;382:1525-1533.
3. Wada N, Jacobson LP, Cohen M, et al. Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008. *Am J Epidemiol*. 2013;177:116-125.
4. Suthar AB, Granich RM, Kato M, et al. Programmatic implications of acute and early HIV infection. *J Infect Dis*. 2015;212:1351-1360.

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5. Lee EJ, Kim YH, Lee JY, et al. Acute HIV-1 infection presenting with fulminant encephalopathy. *Int J STD AIDS*. 2017;28:1041-1044.
6. Ferrada MA, Xie Y, Nuermberger E. Primary HIV infection presenting as limbic encephalitis and rhabdomyolysis. *Int J STD AIDS*. 2015;26:835-836.
7. Vandi G, Calza L, Girometti N, et al. Acute onset myopericarditis as unusual presentation of primary HIV infection. *Int J STD AIDS*. 2017;28:199-201.
8. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach—second edition (available at https://www.who.int). 2016. Accessed February 1, 2019.
9. Althoff KN, McGinnis KA, Wyatt CM, et al. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected vs uninfected adults. *Clin Infect Dis*. 2015;60(4):627-638.
10. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013:1-9.
11. Lanoy E, Spano JP, Bonnet F, et al. The spectrum of malignancies in HIV-infected patients in 2006 in France: the ONCOVIH study. *Int J Cancer*. 2011;129:467-475.
12. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med*. 2011;183:388-395.
13. Sigel K, Wisnivesky J, Gordon K, et al. HIV as an independent risk factor for incident lung cancer. *AIDS*. 2012;26:1017-1025.
14. Hleyhel M, Belot A, Bouvier AM, et al. Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS C04 Cohort. *Clin Infect Dis*. 2013;57:1638-1647.
15. Hart BB, Nordell AD, Okulicz JF, et al. Inflammation-related morbidity and mortality among HIV-positive adults: how extensive is it? *J Acquir Immune Defic Syndr*. 2018;77:1-7.
16. Gootenberg DB, Paer JM, Luevano JM, et al. HIV-associated changes in the enteric microbial community: potential role in loss of homeostasis and development of systemic inflammation. *Curr Opin Infect Dis*. 2017;30:31-43.
17. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014;384:241-248.
18. Wachter RM, Luce JM, Turner J, et al. Intensive care of patients with the acquired immunodeficiency syndrome: outcome and changing patterns of utilization. *Am Rev Respir Dis*. 1986;134:891-896.
19. Schein R, Fischl M, Pitchenik AE, et al. ICU survival of patients with the acquired immunodeficiency syndrome. *Crit Care Med*. 1986;14:1026-1027.
20. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323:1451-1457.
21. Wachter RM, Russi MB, Bloch DA, et al. *Pneumocystis carinii* pneumonia and respiratory failure in AIDS. Improved outcomes and increased use of intensive care units. *Am Rev Respir Dis*. 1991;143:251-256.
22. Palacios R, Hidalgo A, Reina C, et al. Effect of antiretroviral therapy on admissions of HIV-infected patients to an intensive care unit. *HIV Med*. 2006;7:193-196.
23. Powell K, Davis JL, Morris AM, et al. Survival for patients with HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest*. 2009;135(1):11-17.
24. Dickson SJ, Batson S, Copas AJ, et al. Survival of HIV-infected patients in the intensive care unit in the era of highly active antiretroviral therapy. *Thorax*. 2007;62:964-968.
25. Coquet I, Pavie J, Palmer P, et al. Survival trends in critically ill HIV-infected patients in the highly active antiretroviral therapy era. *Crit Care*. 2010;14:R107.
26. Vargas-Infante YA, Guerrero ML, Ruiz-Palacios GM, et al. Improving outcome of human immunodeficiency virus-infected patients in a Mexican intensive care unit. *Arch Med Res*. 2007;38:827-833.
27. Croda J, Croda MG, Neves A, et al. Benefit of antiretroviral therapy on survival of human immunodeficiency virus-infected patients admitted to an intensive care unit. *Crit Care Med*. 2009;37:1605-1611.
28. Turtle L, Vyakernam R, Menon-Johansson A, et al. Intensive care usage by HIV-positive patients in the HAART era. *Interdiscip Perspect Infect Dis*. 2011;2011:847835.
29. van Lelyveld SF, Wind CM, Mudrikova T, et al. Short- and long-term outcome of HIV-infected patients admitted to the intensive care unit. *Eur J Clin Microbiol Infect Dis*. 2011;30:1085-1093.
30. Morquin D, Le Moing V, Mura T, et al. Short- and long-term outcomes of HIV-infected patients admitted to the intensive care unit: impact of antiretroviral therapy and immunovirological status. *Ann Intensive Care*. 2012;2:25.
31. Japiassu AM, Amancio RT, Mesquita EC, et al. Sepsis is a major determinant of outcome in critically ill HIV/AIDS patients. *Crit Care*. 2010;14:R152.
32. Chiang HH, Hung CC, Lee CM, et al. Admissions to intensive care unit of HIV-infected patients in the era of highly active antiretroviral therapy: etiology and prognostic factors. *Crit Care*. 2011;15:R202.
33. Akgun KM, Tate JP, Pisani M, et al. Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era. *Crit Care Med*. 2013;41:1458-1467.
34. Barbier F, Roux A, Canet E, et al. Temporal trends in critical events complicating HIV infection: 1999-2010 multicentre cohort study in France. *Intensive Care Med*. 2014;40(12):1906-1915.
35. Xiao J, Zhang W, Huang Y, et al. Etiology and outcomes for patients infected with HIV in intensive care units in a tertiary care hospital in China. *J Med Virol*. 2015;87:366-374.
36. Kwizera A, Nabukenya M, Peter A, et al. Clinical characteristics and short-term outcomes of HIV patients admitted to an African intensive care unit. *Crit Care Res Pract*. 2016;2016:2610873.
37. Akgun KM, Gordon K, Pisani M, et al. Risk factors for hospitalization and medical intensive care unit (MICU) admission among HIV-infected veterans. *J Acquir Immune Defic Syndr*. 2013;62:52-59.
38. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*. 2001;344:481-487.
39. Davis JL, Morris A, Kallet RH, et al. Low tidal volume ventilation is associated with reduced mortality in HIV-infected patients with acute lung injury. *Thorax*. 2008;63:988-993.
40. Miller RF, Allen E, Copas A, et al. Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. *Thorax*. 2006;61:716-721.
41. Lemiale V, Resche-Rigon M, Mokart D, et al. High-flow nasal cannula oxygenation in immunocompromised patients with acute hypoxemic respiratory failure. *Crit Care Med*. 2017;45:e274-e280.
42. Azoulay E, Lemiale V, Mokart D, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. *JAMA*. 2018;320:2099-2107.
43. Collett LW, Simpson T, Camporota L, et al. The use of extracorporeal membrane oxygenation in HIV-positive patients with severe respiratory failure: a retrospective observational case series. *Int J STD AIDS*. 2019;30(4):316-322.

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44. Obata R, Azuma K, Nakamura I, et al. Severe acute respiratory distress syndrome in a patient with AIDS successfully treated with veno-venous extracorporeal membrane oxygenation: a case report and literature review. *Acute Med Surg*. 2018;5:384-389.
45. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock, 2016. *Intensive Care Med*. 2017;43:304-377.
46. Adlakha A, Pavlou M, Walker DA, et al. Survival of HIV-infected patients admitted to the intensive care unit in the era of highly active antiretroviral therapy. *Int J STD AIDS*. 2011;22:498-504.
47. Mongardon N, Geri G, Deye N, et al. Etiologies, clinical features and outcome of cardiac arrest in HIV-infected patients. *Int J Cardiol*. 2015;201:302-307.
48. Mendez-Tellez PA, Damluji A, Ammerman D, et al. Human immunodeficiency virus infection and hospital mortality in acute lung injury patients. *Crit Care Med*. 2010;38:1530-1535.
49. Medrano J, Alvaro-Meca A, Boyer A, et al. Mortality of patients infected with HIV in the intensive care unit (2005 through 2010): significant role of chronic hepatitis C and severe sepsis. *Crit Care*. 2014;18:475.
50. Cribbs SK, Tse C, Andrews J, et al. Characteristics and outcomes of HIV-infected patients with severe sepsis: continued risk in the post-highly active antiretroviral therapy era. *Crit Care Med*. 2015;43:1638-1645.
51. Huson MA, Scicluna BP, van Vught LA, et al. The impact of HIV co-infection on the genomic response to sepsis. *PLoS One*. 2016;11:e0148955.
52. Wiewel MA, Huson MA, van Vught LA, et al. Impact of HIV infection on the presentation, outcome and host response in patients admitted to the intensive care unit with sepsis; a case control study. *Crit Care*. 2016;20:322.
53. Amancio FF, Lambertucci JR, Cota GF, et al. Predictors of the short- and long-term survival of HIV-infected patients admitted to a Brazilian intensive care unit. *Int J STD AIDS*. 2012;23:692-697.
54. Barbier F, Coquet I, Legriel S, et al. Etiologies and outcome of acute respiratory failure in HIV-infected patients. *Intensive Care Med*. 2009;35:1678-1686.
55. Sonneville R, Ferrand H, Tubach F, et al. Neurological complications of HIV infection in critically ill patients: clinical features and outcomes. *J Infect*. 2011;62:301-308.
56. Roux A, Canet E, Valade S, et al. *Pneumocystis jirovecii* pneumonia in patients with or without AIDS, France. *Emerg Infect Dis*. 2014;20:1490-1497.
57. Lanoix JP, Gaudry S, Flicoteaux R, et al. Tuberculosis in the intensive care unit: a descriptive analysis in a low-burden country. *Int J Tuberc Lung Dis*. 2014;18:581-587.
58. Schmidt M, Sonneville R, Schnell D, et al. Clinical features and outcomes in patients with disseminated toxoplasmosis admitted to intensive care: a multicenter study. *Clin Infect Dis*. 2013;57:1535-1541.
59. Segal LN, Methe BA, Nolan A, et al. HIV-1 and bacterial pneumonia in the era of antiretroviral therapy. *Proc Am Thorac Soc*. 2011;8:282-287.
60. Cilloniz C, Torres A, Polverino E, et al. Community-acquired lung respiratory infections in HIV-infected patients: microbial aetiology and outcome. *Eur Respir J*. 2014;43:1698-1708.
61. Cilloniz C, Torres A, Manzardo C, et al. Community-acquired pneumococcal pneumonia in virologically suppressed HIV-infected adult patients: a matched case-control study. *Chest*. 2017;152(2):295-303.
62. Benito N, Moreno A, Miro JM, et al. Pulmonary infections in HIV-infected patients: an update in the 21st century. *Eur Respir J*. 2012;39:730-745.
63. Cilloniz C, Miguel-Escuder L, Pedro-Bonet ML, et al. Community-acquired *Legionella* pneumonia in human immunodeficiency virus-infected adult patients: a matched case-control study. *Clin Infect Dis*. 2018;67:958-961.
64. Mandell LA, Wunderink R, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44:S27-S72.
65. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000-2010. *J Infect Dis*. 2016;214:862-872.
66. Radhi S, Alexander T, Ukwu M, et al. Outcome of HIV-associated *Pneumocystis pneumonia* in hospitalized patients from 2000 through 2003. *BMC Infect Dis*. 2008;8:118.
67. Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. https://aidsinfo.nih.gov/guidelines. Accessed December 15, 2018.
68. Alanio A, Hauser PM, Lagrou K, et al. ECIL guidelines for the diagnosis of *Pneumocystis jirovecii* pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother*. 2016;71:2386-2396.
69. Morris A, Wei K, Afshar K, et al. Epidemiology and clinical significance of pneumocystis colonization. *J Infect Dis*. 2008;197:10-17.
70. Fauchier T, Hasseine L, Gari-Toussaint M, et al. Detection of *Pneumocystis jirovecii* by quantitative PCR to differentiate colonization and pneumonia in immunocompromised HIV-positive and HIV-negative patients. *J Clin Microbiol*. 2016;54:1487-1495.
71. Louis M, Guitard J, Jodar M, et al. Impact of HIV infection status on interpretation of quantitative PCR for detection of *Pneumocystis jirovecii*. *J Clin Microbiol*. 2015;53:3870-3875.
72. Li WJ, Guo YL, Liu TJ, et al. Diagnosis of pneumocystis pneumonia using serum (1-3)-beta-D-glucan: a bivariate meta-analysis and systematic review. *J Thorac Dis*. 2015;7:2214-2225.
73. Onishi A, Sugiyama D, Kogata Y, et al. Diagnostic accuracy of serum 1,3-beta-D-glucan for *Pneumocystis jirovecii* pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. *J Clin Microbiol*. 2012;50:7-15.
74. Alvarez-Martinez MJ, Miro JM, Valls ME, et al. Prevalence of dihydropteroate synthase genotypes before and after the introduction of combined antiretroviral therapy and their influence on the outcome of Pneumocystis pneumonia in HIV-1-infected patients. *Diagn Microbiol Infect Dis*. 2010;68:60-65.
75. Ewald H, Raatz H, Boscacci R, et al. Adjunctive corticosteroids for *Pneumocystis jirovecii* pneumonia in patients with HIV infection. *Cochrane Database Syst Rev*. 2015:CD006150.
76. Poulakou G, Bassetti M, Timsit JF. Critically ill migrants with infection: diagnostic considerations for intensive care physicians in Europe. *Intensive Care Med*. 2016;42:245-248.
77. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363:1005-1015.
78. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis*. 2018;18:76-84.
79. Critchley JA, Young F, Orton L, et al. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2013;13:223-237.
80. Yang JY, Han M, Koh Y, et al. Effects of corticosteroids on critically ill pulmonary tuberculosis patients with acute respiratory failure: a propensity analysis of mortality. *Clin Infect Dis*. 2016;63:1449-1455.
81. Sonneville R, Schmidt M, Messika J, et al. Neurologic outcomes and adjunctive steroids in HIV patients with severe cerebral toxoplasmosis. *Neurology*. 2012;79:1762-1766.
82. Sonneville R, Magalhaes E, Meyfroidt G. Central nervous system infections in immunocompromised patients. *Curr Opin Crit Care*. 2017;23:128-133.
83. Cantier M, Morisot A, Guerot E, et al. Functional outcomes in adults with tuberculous meningitis admitted to the ICU: a multicenter cohort study. *Crit Care*. 2018;22:210.

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84. Maynard-Smith L, Larke N, Peters JA, et al. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis*. 2014;14:709.

85. Heemskerk AD, Donovan J, Thu DDA, et al. Improving the microbiological diagnosis of tuberculous meningitis: a prospective, international, multicentre comparison of conventional and modified Ziehl-Neelsen stain, GeneXpert, and culture of cerebrospinal fluid. *J Infect*. 2018;77:509-515.

86. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374:124-134.

87. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4: CD002244.

88. Day JN, Chau TT, Lalloo DG. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. 2013;368:2522-2523.

89. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374:542-554.

90. van Veen KE, Brouwer MC, van der Ende A, et al. Bacterial meningitis in patients with HIV: a population-based prospective study. *J Infect*. 2016;72:362-368.

91. Gutierrez J, Albuquerque ALA, Falzon L. HIV infection as vascular risk: a systematic review of the literature and meta-analysis. *PLoS One*. 2017;12:e0176686.

92. Popovich KJ, Weinstein RA, Aroutcheva A, et al. Community-associated methicillin-resistant *Staphylococcus aureus* and HIV: intersecting epidemics. *Clin Infect Dis*. 2010;50:979-987.

93. Huson MA, Stolp SM, van der Poll T, et al. Community-acquired bacterial bloodstream infections in HIV-infected patients: a systematic review. *Clin Infect Dis*. 2014;58:79-92.

94. Sogaard OS, Reekie J, Ristola M, et al. Severe bacterial non-AIDS infections in HIV-positive persons: incidence rates and risk factors. *J Infect*. 2013;66:439-446.

95. Buyse S, Teixeira L, Galicier L, et al. Critical care management of patients with hemophagocytic lymphohistiocytosis. *Intensive Care Med*. 2010;36:1695-1702.

96. Sanchez TH, Brooks JT, Sullivan PS, et al. Bacterial diarrhea in persons with HIV infection, United States, 1992-2002. *Clin Infect Dis*. 2005;41:1621-1627.

97. Imlay H, Kaul D, Rao K. Risk factors for *Clostridium difficile* infection in HIV-infected patients. *SAGE Open Med*. 2016;4: 2050312116684295.

98. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10:251-261.

99. Manzardo C, Guardo AC, Letang E, et al. Opportunistic infections and immune reconstitution inflammatory syndrome in HIV-1-infected adults in the combined antiretroviral therapy era: a comprehensive review. *Expert Rev Anti Infect Ther*. 2015;13:751-767.

100. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4:e5575.

101. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362:697-706.

102. Abdool Karim SS, Naidoo K, Grobler A, et al. Integration of antiretroviral therapy with tuberculosis treatment. *N Engl J Med*. 2011;365:1492-1501.

103. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365:1471-1481.

104. Meybeck A, Lecomte L, Valette M, et al. Should highly active antiretroviral therapy be prescribed in critically ill HIV-infected patients during the ICU stay? A retrospective cohort study. *AIDS Res Ther*. 2012;9:27.

105. Andrade HB, Shinotsuka CR, da Silva IRF, et al. Highly active antiretroviral therapy for critically ill HIV patients: a systematic review and meta-analysis. *PLoS One*. 2017;12: e0186968.

106. Akgun KM, Miller RF. Critical care in human immunodeficiency virus-infected patients. *Semin Respir Crit Care Med*. 2016;37:303-317.

107. El-Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355: 2283-2296.

108. Harding R. Palliative care as an essential component of the HIV care continuum. *Lancet HIV*. 2018;5:e524-e530.

109. Madan S, Patel SR, Saeed O, et al. Outcomes of heart transplantation in patients with human immunodeficiency virus. *Am J Transplant*. 2019;19(5):1529-1535.

110. Sawinski D, Bloom RD. Current status of kidney transplantation in HIV-infected patients. *Curr Opin Nephrol Hypertens*. 2014;23:619-624.

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